"THE CONCORDANCE OF MINOR SALIVARY GLAND HISTOLOGY WITH THE CLINICAL PARAMETERS IN PATIENTS WITH A PROVISIONAL DIAGNOSIS OF SJOGREN'S SYNDROME"

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BRANCH – VI

ORAL PATHOLOGY & MICROBIOLOGY

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DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation entitled "**The Concordance of Minor Salivary Gland Histology with the Clinical Parameters in Patients With a Provisional Diagnosis of Sjogren's Syndrome**" is a bonafide work done under the supervision of **Dr. I. Ponniah, MDS.,** Associate Professor & HOD, Department of Oral Pathology and Microbiology, Tamil Nadu Government Dental College and Hospital, Chennai - 600 003. I also declare that this work was done after careful and thorough analysis not amounting to any sort of plagiarisms or ethical deviations.

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This is to certify that the dissertation entitled **"The Concordance of Minor Salivary Gland Histology with the Clinical Parameters in Patients With a Provisional Diagnosis of Sjogren's Syndrom**e" is a bonafide work done by **Dr. CHAKSHU AGGARWAL** towards the partial fulfillment of the requirement for the degree of **MASTER OF DENTAL SURGERY** in the specialty of **ORAL PATHOLOGY AND MICROBIOLOGY (Branch VI),** under my supervision.

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ENDORSEMENT BY THE PRINCIPAL / HEAD OF THE INSTITUTION

This is to certify that the dissertation entitled **"The Concordance of Minor Salivary Gland Histology with the Clinical Parameters in Patients With a Provisional Diagnosis of Sjogren's Syndrome"** is a bonafide work done by **Dr. CHAKSHU AGGARWAL** under the supervision of **Dr. I. Ponniah, MDS.,** Associate Professor & HOD, Department of Oral Pathology and Microbiology, Tamil Nadu Government Dental College and Hospital, Chennai – 600 003.

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DECLARATION

I **Dr. Chakshu Aggarwal**, do hereby declare that the dissertation titled **"The Concordance of Minor Salivary Gland Histology with the Clinical Parameters in Patients With a Provisional Diagnosis of Sjogren's Syndrome"** was done on the cases of provisional diagnosis of Sjogren syndrome who reported between Jan-1 -09 to July-30-09 to Department of Oral Pathology, Tamil Nadu Government Dental College & Hospital, Chennai 600 003 in partial fulfillment of the requirements for the degree of **Master of Dental Surgery** in the specialty of **Oral Pathology & Microbiology (Branch VI)** during the course period 2007-2010 under the supervision of**, Dr. I. Ponniah, MDS.**

I declare that no part of the dissertation will be utilized for gaining financial assistance for research or other promotions without obtaining prior permission from the Tamil Nadu Government Dental College & Hospital.

I also declare that no part of this work will be published either in the print or electronic media except with those who have been actively involved in this dissertation work and I firmly affirm that the right to preserve or publish this work rests solely with the prior permission of the Principal, Tamil Nadu Government Dental College & Hospital, Chennai 600 003, but with the vested right that I shall be cited as the author(s).

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Dr. Chakshu Aggarwal

ABSTRACT

Objective:

The objective of this prospective study was to evaluate the minor salivary gland histology of patients with a provisional diagnosis of Sjogren's syndrome in relation to clinical parameters to determine the level of correlation in patients with and without Sjogren's syndrome.

Material and methods:

A total of 71 cases with provisional diagnosis of Sjogren's syndrome were studied who reported between Jan 2009 till July 2009 in the Department of Oral and Maxillofacial Pathology, Tamil Nadu Government Dental College and Hospital, Chennai, India for the histopathological evaluation of minor salivary gland lobules.

Results:

About 25% cases having provisional Sjogren syndrome were diagnosed as definite Sjogren's syndrome positive. Sjogren's syndrome affected older age group and showed characteristic female predilection compared to non-Sjogren's cases. Clinical features of xerostomia and keratoconjuctivitis sicca were seen in both Sjogren's syndrome positive and negative cases with more expression in Sjogren's syndrome cases. Both showed degenerative changes on histopathological evaluation of minor salivary glands but a better correlation was found between clinical and histological features in non Sjogren's cases when compared to Sjogren's syndrome cases.

Conclusion:

Correlation was found between histological and clinical features in Sjogren's syndrome, but it was not consistently present in all the cases. Hence diagnosis of Sjogren's syndrome should be rendered carefully after observing clinical features and histological features.

Key Words:

Sjogren's syndrome, Xerostomia, Keratoconjunctivitis sicca, Pathology, Histology, Chennai, Tamil Nadu.

CONTENTS

ABBREVIATIONS

AD:	Acinar Degeneration
AT:	Adipose Tissue
DE:	Ductal Ectasia
DP:	Ductal Proliferation
FI:	Focal Inflammation
GC:	Germinal Center
IF:	Interstitial Fibrosis
KCS:	Keratoconjuctivitis Sicca
MSG:	Minor Salivary Gland
MSGB:	Minor Salivary Gland Biopsy
NPV:	Negative Predictive Value
PPV:	Positive Predictive Value
pSS:	Primary Sjogren'syndrome
SI:	Scattered Inflammation
SS:	Sjogren's Syndrome
sSS:	Secondary Sjogren's Syndrome
USWF:	Unstimulated Whole Salivary Flow

Introduction

INTRODUCTION

Sjogren's syndrome (SS) is a chronic inflammatory autoimmune disorder characterized by lymphocytic infiltration of exocrine glands and symptoms of persistent oral and ocular dryness. The symptoms can occur alone, termed as primary Sjogren's syndrome, or in association with other autoimmune diseases such as systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA) referred to as secondary Sjogren's syndrome. It is among the three most commonly occurring autoimmune disorders in RA and SLE and is almost equal to or behind RA in prevalence. [1- 3] Though reported to be common disease in western countries, very few reports has been published from our country.[4-5] Prevalence of SS ranges from 0.1% to 4% due to various classifications used for the diagnosis. [1-3, 6-7] It is more prevalent in middle aged females. Primary SS shows two age peaks, first after menarche and the second peak after menopause. Female to male ratio ranges from 9:1 to 24:1. [8-10]

No single instrumental or laboratory parameter is available for the diagnosis of Sjogren's syndrome. Diagnosis relies on evaluation of multiple parameters which include subjective symptoms of dryness in eyes and oral cavity, various tests like Resting salivary flow, Parotid flow and Schirmer's test, Rose Bengal test, Tear breakup time test are done for the objective signs of xerostomia and keratoconjunctivitis respectively. Investigatory procedures like serological levels of antibodies like rheumatoid factor, antinuclear antibodies, SS-A and SS-B and histopathological evaluation of major and minor salivary glands for inflammation are done to diagnose a case of Sjogren's syndrome.[11]

The presence of chronic focal inflammatory infiltrates in lip salivary glands, as assessed with minor salivary gland biopsy (MSGB), is one of the parameters included in most criteria sets proposed for SS classification.[12-16]

Currently used criteria to classify patients affected by Sjogren's syndrome depends on demonstration of dry eyes, dry mouth, focal collection of inflammatory infiltrate in salivary gland biopsy and on the presence of auto antibodies in the serum.[2]

This condition has been studied for over 100 yrs. [3,11] The labial salivary gland biopsy has been considered as an important parameter among others to help confirm the SS diagnosis for long.[11] A characteristic histopathologic feature in minor salivary glands in Sjogren's syndrome is focal lymphocytic sialadenitis. Focal lymphocytic infiltrates of minor salivary glands are considered target-organ specific signs of SS.[17-18] With time, the diagnostic significance of the labial salivary gland biopsy has increased and it has been anecdotally referred to as "the gold standard" by some physicians.[19-20] The AECG criteria require either positive auto-antibodies (anti Ro/SS-A or anti-La/SS-B) or a positive LSG biopsy to confirm SS diagnosis.

Till now, inflammatory cells foci is considered to be an important criteria, presence of focus is characteristic but not diagnostic as it can be found in healthy individuals, sialolithiasis, myasthenia and various connective tissue diseases and is not always present in all cases of Sjogren's syndrome. [21- 24]

Evaluation of histopathological features in MSGB of SS can pose diagnostic difficulty with chronic sialadenitis. MSGB is major criteria in AECG and a false diagnosis can adversely affect the patient condition. There is less awareness among the oral pathologist/ dentists in India about SS, though dentists can be the first person to encounter a case of SS due to rarity in reporting of SS cases. [25-26] Literature from India is less. Usually the histopathological picture of cases of SS is not consistent in all the cases and exhibits various histological features and show a range of clinical features ranging from extraglandular to systemic features.[20 22]

Serological investigation of antibodies specific to SS, though is a major criteria, is not cost effective and it is difficult to get this investigatory procedure in a government setup where most of the patients reporting are low income group patients. It is not always positive in all the cases of SS [21].

Thereby, we are evaluating the MSGB and trying to determine the level of correlation present between the clinical features with which the patient is presenting and various histological parameters seen in MSG like acinar degeneration, ductal proliferation, ductal ectasia, vascularity, presence of inflammatory foci, germinal center formation and diffuse inflammation, fat component, giant cells in addition to lymphocytic foci in suspected cases of SS.

Aims and objectives

AIMS AND OBJECTIVES

Aim:

To evaluate the minor salivary gland histology of patients with a provisional diagnosis of Sjogren's syndrome in relation to clinical parameters.

Objectives:

To determine the level of correlation in patients with and without Sjogren's syndrome.

Review of Literature

Greenspan JS et al 1974 [27]studied labial salivary gland biopsies in patients with definite SS and control cases and reported the advantages of a focus scoring method for evaluating severity of involvement. They concluded that focus score was a valuable histological index for severity of salivary gland involvement in this disease and cases with more foci had larger foci. Higher focus score also correlated with acinar depletion but not with duration of disease. Few cases of SS with low focus score had marked loss of acini which had been replaced by fibrosis or by fat. Both intralobular and interlobular ducts showed varying degrees of dilatation, thickening or thinning of the lining epithelium and oncocytic change in the epithelial cells. However, these changes did not bear any clear relationship to the infiltrative and destructive processes. Of the control cases, 18% showed a labial gland grade of 0, 29% a grade of 1, 42% a grade of 2 and 11% a grade of 3. Foci were seen always in relation to duct dilation, extravasation of saliva, or extra vascular polymorphs.

Scott J. 1980 [28] studied histologically non-diseased labial salivary glands from 70 necropsies evenly divided by sex and age between 18-90 years. They studied a limited number of morphometric features in sublabial salivary gland tissue and showed that atrophy of acini, fibrosis, and ductal hyperplasia also occur in the minor salivary glands with aging and affected females earlier than males. Only a quarter of the series contained foci of lymphorecticular cells mostly in lobules affected by parenchymal atrophy, dilatation and hyperplasia hence, they concluded that the prevalence of lymphoplasmacytic infiltrate was unrelated to age.

Drummond JR and Chisholm DM 1984 [29]studied a series of 36 post-mortem labial salivary glands from both male and female subjects with ages ranging from 25 to 80 year. Acinar atrophy, fibrous replacement, diffuse infiltrates of lymphocytes,

ductal aberrations and oncocytic change in some were noted in the aged glands. Ductal dilatation and hyperplasia were also common. No simple correlation was found between focal sialadenitis and the age and sex of the patient. Obstructive sialadenitis characterized by acinar atrophy, duct hyperplasia, fibrous replacement and diffuse chronic inflammatory infiltrates was observed in the labial glands and showed an increasing severity with age.

Daniels TE, 1984 [30] studied Labial salivary gland biopsies in 362 suspected cases of Sjögren's syndrome. He concluded that areas of labial salivary gland that show duct ectasia, fibrosis and diffuse acinar atrophy were nonspecific degenerative changes that were often age related and should be excluded from focus scoring.

Segerberg-Konttinen M et al, 1986 [24] studied retrospectively a slide library and found that conditions other than SS also resulted in FS more than 1. In 8/17 patients, sialolithiasis of the submandibular glands was associated with focus scores of greater than 1, usually with little or no histological signs of obstruction and/or infection. Focus score values of greater than 1 were found in the labial salivary glands in 6/40 (15%) coroner's autopsies although the subjects had no clinical history or findings suggesting SS; simultaneous specific involvement of both salivary and lacrimal glands was however, not observed in the subjects. They suggested that a postmortem diagnosis of SS should be made on the demonstration of focus score of greater than 1 in both the labial salivary glands and the lacrimal glands.

The sublabial salivary glands were studied by morphometric methods by **Dewilde PCM 1986** [23] in 68 healthy volunteers to establish possible changes related to age in those tissue components that are affected in Sjogren's syndrome and connective tissue diseases (which might simulate Sjogren's syndrome). There was an

increase in the amount of connective tissue and intralobular ducts with age and a corresponding decrease in acinar tissue. The amount of diffuse lymphoplasmacytic infiltrate and the vascularity of the tissue remained constant with age. In 22% of subjects lymphocytic foci were seen, 40% of these had a score >1 focus suggestive of Sjogren's syndrome. The aging process was accompanied by atrophy of acini and increase in fibrosis. Intralobular ductal hyperplasia was also observed with aging.

Jacobsson LT et al 1989 [31]**,** studied 705 randomly selected subjects, aged 52-72 years who answered a simple questionnaire, and of whom 247 (35%) reported symptoms of dry eyes or dry mouth.

Segerberg-Konttinen M et al 1989 [32] **,** conducted a postmortem study 102 consecutive medico legal post-mortem subjects to identify signs of focal adenitis in labial, submandibular, and lacrimal glands. There were 19 subjects (18.6%) with focus scores exceeding 1 in one or two types of the glands. Among the 19, five had a disease which is generally associated with Sjögren's syndrome or is autoimmune in nature. He found that fibrosis, atrophy, and fatty change occurred most often in the labial salivary glands in those over 50 years of age with or without high focus scores.

Shah F et al 1992[33]**,** investigated the association between labial salivary gland histopathological changes and the clinical and serologic features of 192 patients with suspected connective tissue disorders. There were significant associations between positive findings on lip biopsy and the presence of keratoconjunctivitis sicca and positive Ro antibodies. In patients with LSG focus scores > 1, approx 50% had parotid gland enlargement. Significant associations were found between LSG focus scores > 1 and KCS. There was no significant association between an LSG focus score of 1 and sicca, KCS or glandular enlargement. The sensitivity of the Ro

response for the presence of sialadenitis was low (0.485) but the specificity was high (0.967). Whereas, sicca symptoms were neither predictive (0.459), nor specific (0.379) but extremely sensitive (0.746) for focal sialadenitis. Salivary or lacrimal gland enlargement was likewise not predictive (0.558) or sensitive (0.492) for focal sialadenitis. A positive ANA result was associated with a focus score of 1 (P=0.018). Anti-Ro antibody was strongly associated (P=0.0001) and was very specific (0.960) for a focus score of 1.

Speight PM et al, 1992 [34]studied unstimulated salivary flow in different age groups and found that 70% of patients with Sjogren's syndrome had decreased flow. They found that unstimulated flow of 0-1 ml.min or less is highly specific for Sjogren's syndrome. They also found that salivary flow was higher in patients with rheumatoid disease and secondary SS as compared to primary SS. However, they found no significant correlation between unstimulated flow rate and focus score.

Coll J et al in 1992 [35]investigated 142 patients (62 with definite Sjogren's syndrome, 24 with probable Sjogren's syndrome, and 56 control cases). Definite keratoconjunctivitis sicca was present in 34 patients (24%) and xerostomia in 56 (39%) whereas both were present in 28 patients (20%). They however, also found 10% of the control subjects with a positive Schirmer's test.

Daniels TE, et al in 1994 [36] studied LSG biopsy specimens from 618 patients with suspected SS to determine the association between patterns of inflammation in labial salivary glands (LSG) and the ocular component of Sjogren's Syndrome(SS). They found a stronger KCS association in patients whose LSG biopsies showed focal inflammation and chronic sialadenitis to be a common feature of labial salivary glands which is neither associated with SS nor an end stage of SS.

Vitali C et al 1994 [12], tested sensitivity and specificity of tests for ocular and oral involvement in Sjogren's syndrome. Data from 22 centers and 11 countries was collected on a total of 447 patients with SS (246 with primary SS and 201 with secondary SS) and 246 controls (of whom 113 had a connective tissue disease without SS). Among the ocular tests, Schirmer's test showed the best balance between sensitivity and specificity (76.9% and 72.4%). The oral tests (except USWC) were generally more reliable than the ocular tests in diagnosing SS. USWC had a sensitivity and a specificity of 56.1% and 80.7%, respectively, with >1.5 ml of saliva collected in 15 minutes being considered the normal limit. Abnormal results for all of the ocular and oral were less frequent and less marked in patients with secondary SS. MSGB (where the presence of at least one inflammatory focus was considered as indicative for the diagnosis) showed a good balance between sensitivity and specificity (82.4% and 86.2%, respectively). The agreement between USWC and MSGB was somewhat lower; if one considered as diagnostic score of ≥1.The presence of inflammatory foci in lip biopsies of patients without SS did not appear to be significantly correlated with age. They showed that both acinar fibrosis and ductal abnormalities were linked to progressive, age-related involution of the minor salivary glands, and that they were observed in equal numbers of patients with and without SS. The number of foci found in patients with primary SS was significantly higher than that observed in patients with SS associated with other CTD. The quantity of inflammatory infiltrates was considerably reduced in the patients with secondary SS associated with RA or with Systemic sclerosis. 25% of those patients with a CTD but not SS had a focus score ≥1. Their study indicated that no single test of oral or ocular involvement was sufficiently sensitive and specific to form the basis for a diagnosis of SS.

Vitali C et al, 1996 [37]undertook a study to assess the European classification criteria for Sjogren's syndrome in a series of clinically defined case. They tested a total of 278 cases (157 SS patients and 121 non-SS controls) collected from 16 centers in 10 countries and found that minor salivary gland biopsy was the most accurate for the diagnosis of SS (89.0 and 84.1 when focus scores - 1 and >1, respectively, were considered as indicative of the diagnosis), followed by parotid sialography (83.3%), and Schirmer's test (77 .0%).

Field EA and coworkers 1997, [38] studied 100 consecutive patients which reported a daily feeling of oral dryness for at least 6 months. On sialometry 39 patients had a low unstimulated flow rate (≤0.1 ml/min) with only 17 patients with complete lack of unstimulated saliva. They suggested that salivary hypofunction and resultant xerostomia were not inevitable consequences of ageing as reductions in salivary flow do not necessarily correlate with diminished oral health. Their study yielded that a complaint of dry mouth does not always result in a diagnosis of SGH, as only 39% of the patients attending the xerostomia clinic were found to have objective evidence of reduced salivary flow and only 40% of patients were diagnosed as SS. However, some individuals with a very low flow rate did not complain of oral dryness and others with copious amounts of saliva felt that they have a dry mouth

Hay EM in 1998 [39] conducted a cross sectional population based survey on 341 subjects to determine associations between symptoms of dry eyes and dry mouth and objective evidence of lacrimal and salivary gland dysfunction in a population based sample. They interviewed for the presence of dry eyes and mouth and examined for Schirmer's test and unstimulated salivary flow rate. They found 24% had dry eye symptoms, 29% dry mouth symptoms, and 14% both. There was only a weak

association between the presence of oral or ocular symptoms and their respective test results. Associations were strongest between dry mouth symptoms and positive test results and in subjects under 55 year (younger) of age.

Skoupouli FN et al in 2000, studied the impact of primary Sjogren's syndrome (pSS) on overall survival in a prospective study of a cohort of 261 patients with pSS. He found that low C4 levels and mixed monoclonal cryoglobulinemia were linked with an approximately 6- to 8-fold relative risk for the development of lymphoma.

Ohara T et al 2000 [40], evaluated the diagnostic value of laboratory parameters in relation to histopathological findings in Sjogren's syndrome (SS) in 96 patients. The percentage of cases with positive assays of rheumatoid factor and anti-SS-A/Ro antibodies was significantly higher in definite SS. 80% of patients with definite SS had specific abnormal findings on histology in salivary glands. However, 20% of patients did not have such findings and were diagnosed as definite SS from specific abnormal findings in sialogram. No useful laboratory parameters were found for the diagnosis of secondary SS. Schirmer's test had a sensitivity of 64% and specificity of 85% in the diagnosis of primary SS. However, no significant correlation for Schirmer's test was observed between the negative SS group and the definite SS group.

Kalk WW et al 2001 assessed the value of glandular sialometry and sialochemistry as diagnostic instruments in SS in a group of 100 consecutive patients referred for diagnosis of SS. Patients were classified as positive or negative for SS according to the revised European classification criteria. Patients with SS differed clearly from those who tested negative for SS, showing lower

submandibular/sublingual (SM/SL) flow rates. Their study resulted that all glandular secretary flow rates were inversely related to duration of oral symptoms in SS group, however, when the disease was still incipient, sialometry might not show any loss of glandular function.

Al-Hashimi I et al in 2001 [41], examined 38 minor salivary gland biopsies to study the reproducibility of biopsy in Sjogren's syndrome. They examined biopsies at 6 mm, 50 mm, 100 mm, 150 mm, 200 mm, and 250 mm tissue depths and found wide range of grade variability at all depths. Their study yielded that no tissue depth was consistently reproducible for any grade.

Dawson LJ et al 2001[42]**,** aimed to determine if the salivary gland hypofunction associated with primary Sjogren's syndrome (SS- 1) is more severe than that associated with secondary Sjogren's syndrome (SS- 2). They retrospectively compared for age and gender matched, patients diagnosed with SS-1 or SS-2 according to the preliminary European criteria. They found no significant differences of unstimulated whole salivary flow rates between individuals with SS-1 or SS-2 and hence concluded that the severity of salivary gland hypofunction does not appear to be related to the clinical variant of Sjogren's syndrome.

Price EJ and Venables PJ 2002 [43] collected clinical, serological and histological data on 34 patients presenting with dry eyes and/or mouth who did not satisfy the Vitali criteria for the diagnosis of SS and compared with 136 patients with primary SS, 38 patients with secondary SS, and 13 patients without SS. Questionnaires on symptoms from each group were compared with 43 healthy controls. They found no evidence that age, salivary gland atrophy or subclinical SS accounted for the symptoms in dry eyes and mouth syndrome.

Rosas J et al, 2002, [44]studied usefulness of basal and pilocarpine-stimulated salivary flow in primary Sjogren's syndrome and their correlation with clinical, immunological and histological features. They investigated the clinical and immunological characteristics of 60 consecutive patients with primary SS which fulfilled four or more of the preliminary diagnostic European criteria for SS. Unstimulated (basal) salivary flow (BSF) was measured in all patients. The mean BSF for SS patients was 1.40±0.17 ml with 83% patients showing a BSF < 1.5 ml.

Radfar L et al, 2002 [45,] studied prevalence and clinical significance of lymphocytic foci in minor salivary glands of 54 healthy volunteers and found 15% with focal lymphocytic infiltrate. None of these individuals had subjective xerostomia or dry eyes. The positive FS ranged from 2 to 6. FS did not correlate with age, smoking, serologic findings, or salivary flow in these patients. They concluded that lymphocytic infiltration in minor salivary glands was not uncommon among individuals without a history of salivary gland dysfunction

Misra R et al 2003 [26], studied 26 patients (21 being women) with dry eyes, dry mouth, and arthritis/arthralgia. Minor salivary gland biopsy provided a definitive diagnosis in 16/26 (60%). The important laboratory abnormalities being hypergammaglobulinaemia (16/20),antinuclear antibodies (18/26), anti-La (11/19) and anti-Ro (10/19). They found that prevalence of primary Sjogren's syndrome was rare even in tertiary care rheumatology clinics in India and the clinical and immunological profile were also similar to that reported in Western countries.

Salomonsson S et al 2003 [46], underwent a study to find out cellular basis of ectopic germinal center (GC) formation and autoantibody production in the target organ of patients with Sjogren's Syndrome. 165 minor salivary gland biopsy samples

from patients of SS were screened for GC-like structures and GC-like structures were observed in 17% of patients. There was no statistically significant difference between occurrence of these structures in patients with primary SS and in those with secondary SS. The GCs formed within the target tissue showed functional features with production of autoantibodies (anti-Ro/SSA and anti-La/SSB) and apoptotic events (by TUNEL staining), and there was increased local production of anti-Ro/SSA and anti-La/SSB autoantibodies ($P = 0.04$) in patients with GC development.

Kikuchi M et al 2004 [47]**,** examined histologically labial, sublingual and submandibular salivary glands from 53 autopsy subjects without any symptoms with an average age of 84 years. They concluded that there was no relationship between degree of lymphocytic infiltration in minor salivary gland and age.

Sánchez-Guerrero J et al 2005 [48] investigated randomly chosen 300 patients from rheumatology and internal medicine clinics to find prevalence of SS. The mean age of the subjects was 42.8±15.7 year. The minimum prevalence of SS in the population studied was found to be 13.3% (95% CI, 9.5–17.1%), primary SS (prevalence 2.7%) and secondary SS (prevalence 10.7%)

Morbini P et al 2005 [49] evaluated a cumulative focus score (cFS) on three slides cut at 200-μm intervals from each of a series of 120 salivary biopsies. The diagnostic performance of AECG classification was significantly improved when the cFS was entered in the AECG classification; the improvement was mostly due to increased specificity in biopsies with a baseline FS ≥ 1 but <2.

Jonsson MV et al 2005 [50] found that lymphoid organization in the shape of ectopic germinal centers were detected in 33 of 130 consecutive minor salivary gland

biopsies of the chronic, autoimmune disorder Sjögren's syndrome and coincided with increased focus score.

Delaleu N et al 2005 [51]**,** said in there paper that despite chronic symptoms of severe oral dryness manifested by a 80-90% decrease in salivary flow compared with normal individuals, the acinar and ductal structures appeared not to be destroyed to such extent and in addition to lymphocytic infiltration, acinar epithelial atrophy, and progressing fibrosis can be observed with glands of patients with SS.

García-Carrasco M et al 2006[52] studied patho-physiology of Sjogren's syndrome. They concluded that degree of glandular destruction and symptoms of dryness do not seem to be directly related to the number of infiltrating lymphocytes.

Venables PJ. 2006 [53] in their study found that sicca symptoms were not fully associated with inflammation as low dose steroid which are capable of reducing inflammation did not improve salivary flow. Salivary gland swelling occurs in about 60% of patients with Sjogren's syndrome, and may affect any of the major or minor salivary glands.

Pijpe J et al, 2007 [54], compared Parotid gland biopsy with labial biopsy in the diagnosis of patients with primary Sjogren's syndrome. A total of 30 labial and parotid biopsies were studied. It was found that the presence of foci, confluence of the infiltrate and fibrosis was comparable in both major and minor salivary glands. Germinal centers were present in four patients, in both labial and parotid biopsies. Lymphoepithelial islands (LEL) were present only in parotid gland tissue, while labial salivary gland tissue showed more atrophy and therefore, in addition to the focus score, benign LELs in the parotid gland can be used as an additional aid in diagnosis. They concluded that a parotid biopsy has a diagnostic potential comparable with that

of a labial biopsy in the diagnosis of pSS, and may be associated with less morbidity in contrast to labial salivary glands.

Jonsson MV et al 2008 [55], retrospectively studied minor salivary gland biopsies with focal lymphoid aggregates corresponding to focus score > 1 fulfilling the American-European criteria for pSS and evaluated for the presence of GC-like morphology. GC-like features were observed in 28% biopsies. Mean inflammatory focus score and frequency of patients with unstimulated salivary secretion ≤1.5ml/15min was significantly higher in GC-positive compared to GC-negative samples. Enlarged salivary glands were observed in 28% patients, without any linkage to presence or absence of GC-like features.

Jonsson MV and Skarstein 2008[55], studied that presence of Follicular dendritic cells confirm lymphoid organization in the minor salivary glands of primary Sjogren's syndrome. A randomly selected cohort of 60 patients who fulfilled the revised American–European criteria for primary SS was investigated in this study. Biopsies with primary SS were investigated for the expression of CD21, CD23, CD35 and IgD by immunohistochemistry. 20% of the biopsies in this random sample had GC-like morphology in the routine H&E tissue section The mean focus score was significantly higher in the GC+ patients ($P < 0.05$).

Mathews SA et al, 2008 [10]studied Oral Manifestations of Sjogren's Syndrome. They found acinar epithelial atrophy and progressing fibrosis within glands of persons with Sjogren's syndrome and in spite of chronic symptoms of serious oral dryness, as seen by 80-90% decrease in salivary flow compared with that in normal individuals, the acinar and ductal structures do not appear to be destroyed to such an extent.

Caporali R et al 2008 [56], underwent a study to investigate safety and usefulness of minor salivary gland biopsy by analyzing retrospectively 452 patients with suspected SS. 93 patients (24.5%) had focal sialadenitis upon histopathologic evaluation; of these, 87 (94.5%) satisfied the AECG criteria set. Only 1.6% of patients who did not have the requisites for the diagnosis of SS had a chronic focal sialadenitis. They concluded that MSGB is a simple, safe, and reliable tool for the diagnosis of SS and amyloidosis, and therefore is suitable for more extensive application

Bamba R et al 2009 [57]**,** retrospectively studied salivary gland biopsies of 46 patients of SS, 39% of these patients had a negative biopsy (grade <3) and 61% had a positive biopsy (grade = 3 or 4). Their study resulted that salivary gland swelling, and abnormal serology (anti-Sjogren syndrome A/anti- Sjogren syndrome B) were more prevalent in the positive lip biopsy group (grade 3 or 4). Out of the 12 patients who had sicca symptoms and positive serology, nine (75%) had grade 4. Presence of sicca symptoms and positive serology were predictive of a positive biopsy ($p < .017$).In their study, clinical presentation of sicca symptoms and positive serology reliably predicted the results of a lip biopsy.

Eliasson L et al 2009 [58]**,** studied 142 individuals, aged 18–82 years. Feelings of oral dryness were assessed and resting whole saliva flow rates were measured by conventional methods. The resting secretion rates were significantly lower in subjects with complaints compared with individuals of no complaints. Also, some individuals with normal secretion rate reported dry mouth feelings. It was suggested that local areas of dry mucosa, with lowered flow of saliva and of mucous production, could trigger a sensation of dry mouth.

Material and Methods

MATERIALS & METHOD

Eighty four consecutive patients who attended the OPD at Tamil Nadu Government Dental College & Hospital, Chennai from a period of Jan 2009 to July 2009 (including both months) were included in this study. The patients were referred under suspicion of SS by rheumatologists, neurologists and medicine physicians. Reasons for referral were not limited to polyarthralgia and connective tissue diseases but also included ocular or oral manifestations such as eye dryness, mouth dryness, swelling of the salivary glands and systemic problems such as neurological disorders. Out of 84 cases 14 cases were excluded due to insufficient data due to various reasons. So, 71 cases were included in the study. The cases were divided into two groups as SS+ve and SS-ve group depending on the diagnosis which was rendered according to the American-European Consensus Group Classification criteria for Sjogren's syndrome (2002).[59]

Clinical Parameters

General patient history regarding age, chief complaints, duration and specifically oral and ocular symptoms were recorded on a performa in a questionnaire format according to the revised American-European criteria 2002.

ASSESSMENT OF THE ORAL COMPONENT

The three questions assessed oral dryness.

Oral symptoms

1. Have you had a daily feeling of dry mouth for more than 3 months?
2. Have you had recurrently or persistently swollen salivary gland as an adult?
3. Do you frequently drink liquid to aid in swallowing dry foods?

Positive response to any of the three confirmed the presence of oral dryness symptom.

Method to collect Unstimulated whole saliva (Sialometry)

Unstimulated whole saliva flow (USWF) was measured by the spitting method. The patients were instructed not to eat, drink, or smoke during 90 minutes preceding the sialometric assessment. The patient was seated comfortably, he or she was instructed to rest for 5 min before the test, minimize orofacial movements and not to speak. Before starting the procedure, but not later, the patient swallowed any residual saliva and was then asked to allow all saliva to accumulate on the floor of the mouth and to spit it gently into a graduated test tube every minute. Saliva was collected for a period of 15 min [34] and the measured volume expressed in ml/15min. The cutoff value on this study was 1.5 ml/15 minutes for the reason that 1.5 ml/15 minutes had been selected as the cutoff value in the American-European Consensus Group Classification criteria for Sjogren's syndrome (2002).[59]

Unstimulated whole salivary flow less than or equal to 1.5ml/15min was considered as positive objective sign for dry mouth.

CLINICAL PARAMETERS

ASSESSMENT OF THE OCULAR COMPONENT

The three questions assessed ocular dryness.

Ocular symptoms:

1. Have you had daily, persistent, troublesome dry eyes for more than 3 months?

2. Do you have recurrent sensation of sand or gravel in the eyes?

3. Do you use a tear substitute more than 3 times a day?

Positive response to any of the three confirmed the presence of ocular dryness symptom.

The Schirmer test

The Schirmer test was carried out in the Government Eye Hospital Egmore, Chennai.

Procedure:

The Schirmer test was carried with a filter-paper strip (Schirmer tear test standardized sterile strips) of 0.5 to 30 mm. The strip was placed in the lower fornix between the medial and lateral third of the eyelid of the unanaesthetized eye. After 5 minutes, the amount of wetting was measured from the extraforniceal position of the strip.[59]

A value of 5 mm or less per 5 minutes was considered as a positive objective criteria for keratoconjunctivitis sicca (KCS).[59]

Patient's medical history especially the presence or absence of connective tissue disease was obtained from the medical records by Department of Rheumatology, Madras Medical College & Government General Hospital, Chennai.

Labial salivary gland biopsy

Labial salivary gland biopsy (LSGB) was performed in the Department of Oral Surgery, Tamil Nadu Government Dental College & Hospital, Chennai as a part of routine diagnostic procedure. Local anesthesia (2 % lidocaine) was injected deep to the glandular tissues of the lower lip. A 1.5 to 2.0 cm linear incision was made in the mucosa, parallel to the vermillion border and lateral to the midline. Following blunt dissection, the margins of the salivary glands were removed individually and placed in fixative. No surface mucosa was removed and the mucosal incision was reapposed with 4-0 braided silk or plain gut sutures. Sutures were removed after 5 to 7 days.[60] Then the specimen was sent for processing and routine H & E staining in Department of Oral Pathology for histopathological evaluation.

MSBG samples were fixed in formalin, processed, and embedded in paraffin according to standardized laboratory methods.

Using the Leica microtome, 4 micron meter thick sections were cut from the blocks for Ehrlich Hematoxylin and Eosin staining.

Procedure for Hematoxylin and Eosin staining[61]

- Sections are deparaffinised with xylene.
- Hydration with descending grades of alcohol.
- The sections are drained and transferred to hematoxylin, where they are left for 10 minutes.
- The slides are then drained and washed in running water until the sections are blue.
- The sections are dipped in acid alcohol where they are agitated for a few seconds and again washed in running water until blue again.
- The sections are counterstained with eosin for 30 seconds.

- The sections are washed in running water for 3-4 minutes, to differentiate the eosin.
- After draining, the sections are dehydrated in ascending grades of alcohol.
- The sections are cleared with xylol, where they are given two changes for 30 seconds each.
- The sections being clear, the slides are dried and mounted with Distrene 80 Dibutyl Phthalate Xylol (DPX) under a coverslip.

  Results

  1. Nuclei: Blue
  2. Cytoplasm: Varying shades of pink
  3. Collagen: Pink

The stained and mounted slides for all cases were examined under the light microscope and following histological parameters were evaluated.

HISTOLOGICAL PARAMETERS

- Apparently normal
- Acinar Degeneration
- Ductal ectasia/ dilatation
- Ductal proliferation
- Squamous metaplasia
- Epimyoepithelial islands
- Inflammatory infiltrate
  - Focal
  - Diffuse
- Germinal centre formation

- Interstitial fibrosis
- Multinucleated giant cells
- Vascular component
- Adipose tissue component

Histological features

Acinar Degeneration

The secretory part of the gland consisting of serous and mucous acini was observed for the presence or absence of degeneration. Total loss or degeneration of acini to duct like structures was considered as degeneration present. The criteria of presence of degeneration were set arbitrarily.

Fibrous tissue

Increase in the connective tissue within the sublabial salivary gland or in the lobules of the salivary gland tissue was considered as present. The fibrous capsule was excluded.

Ductal proliferation

Increase in the number of duct in a given area within the glandular lobules was considered positive. The criteria were set arbitrarily. Larger ducts in the connective tissue, septa, and hilum of a gland were not included.

Ductal ectasia

Increase in the diameter of the intralobular duct was observed and compared relatively to the normally present ducts and increase in the diameter was given as presence of ectasia.

Vascularity

All vessels situated within the lobules were counted in high power fields in all the lobules. Total count of the vessels was divided by the total number of high power fields. The vessels were divided into three groups according to the number of vessels per high power field. The count of vessels per HPF between 0-2 was given as mild, 2-5 as moderate and above 5 as high. The larger vessels in the fibrous septa and hilum were excluded.

Lymphocytic focus

An aggregate of more than 50 lymphocytes and histiocytes, usually with a few peripheral plasma cells constituted a lymphocytic focus. A lymphocytic focus has a great density of inflammatory cells and is usually very well demarcated. The mononuclear infiltrate was classified as focal, when periductal and/or perivascular, and diffuse, when sparsely interspersed with seromucinous cells. These aspects were classified as present or absent. Labial salivary gland biopsies were assessed histologically using criteria initially described by Chisholm and Mason. They defined a focus as an aggregate of at least 50 lymphocytes, and found that more than one focus/4 mm^2 area of gland was seen only in patients with SS.[62]

Germinal center formation

GC-like features were observed as well-circumscribed chronic inflammatory cell infiltrate consisting of at least 50 mononuclear cells, presenting with a densely packed dark zone and a light zone, within otherwise normal salivary gland epithelium.

Scattered inflammation

These consisted of the plasma cells and lymphocytes in the fibrous stroma of the gland and areas of fibrosis. A diffuse infiltrate has a low density of cells, mostly

plasma cells. All other phenomena of inflammatory activity that did not satisfy the definition of a lymphocytic focus were included in the definition of lymphoplasmacytic infiltrate.

Grade scores ranged from 0 to 4 for focal inflammation.

0=absent infiltrate

1=slight infiltrate

2=moderate infiltrate

3=1 focus of at least 50 lymphocytes/4 mm^2 of gland.

4≥1 foci of at least 50 lymphocytes/ 4 mm^2 of gland.

The histological parameter was considered as negative in the absence of any inflammatory infiltrate (FS = 0) and in the presence of less than 1 focus per 4 mm^2 (0 < FS < 1) [59]; the presence of one or more foci per 4 mm^2 was considered positive.

Less-than-optimal tissue area (biopsy section area less than 4 mm^2) was not considered a criterion for exclusion, provided that at least one normotrophic glandular lobule had been sampled.

American-European Consensus Group Classification criteria for Sjogren's syndrome (2002) [59]

I. Ocular symptoms: a positive response to at least one of the following questions:

Have you had daily, persistent, troublesome dry eyes for more than 3 months?

Do you have a recurrent sensation of sand or gravel in the eyes?

Do you use tear substitutes more than 3 times a day?

II. Oral symptoms: a positive response to at least one of the following questions:

Have you had a daily feeling of dry mouth for more than 3 months?

Have you had recurrently or persistently swollen salivary glands as an adult?

Do you frequently drink liquids to aid in swallowing dry food?

III. Ocular signs: objective evidence of ocular involvement defined as a positive result for at least one of the following two tests:

Schirmer's test, performed without anesthesia (<5 mm in 5 minutes)

Rose bengal score or other ocular dye score (>4 according to van Bijsterveld's scoring system)

IV. Histopathology: In minor salivary glands focal lymphocytic sialoadenitis, evaluated by an expert histopathologist, with a focus score >1, defined as a number of lymphocytic foci per 4 mm^2 of glandular tissue

V. Salivary gland involvement: objective evidence of salivary gland involvement defined by a positive result for at least one of the following diagnostic tests:

Unstimulated whole salivary flow (<1.5 ml in 15 minutes)

Parotid Sialography showing the presence of diffuse sialectasias without evidence of obstruction in the major ducts

Salivary scintigraphy showing delayed uptake, reduced concentration and/or delayed excretion of tracer

VI. Autoantibodies: presence in the serum of the following autoantibodies:

Antibodies to Ro(SSA) or La(SSB) antigens, or both

For primary SS

In patients without any potentially associated disease, primary SS may be defined as follows:

The presence of any 4 of the 6 items is indicative of primary SS, as long as either item IV (Histopathology) or VI (Serology) is positive

The presence of any 3 of the 4 objective criteria items (that is, items III, IV, V, VI)

For secondary SS

In patients with a potentially associated disease (for instance, another well defined connective tissue disease), the presence of item I or item II plus any 2 from among items III, IV, and V may be considered as indicative of secondary SS

Exclusion criteria:

Past head and neck radiation treatment

Hepatitis C infection

Acquired immunodeficiency disease (AIDS), Pre-existing lymphoma

Sarcoidosis

Graft versus host disease

Use of anticholinergic drugs (since a time shorter than 4-fold the half life of the drug)

Observations & Results

A Total 71 cases were studied and 18(25.4%) cases were found SS positive. Remaining 53(74.6%) cases were diagnosed SS –ve.

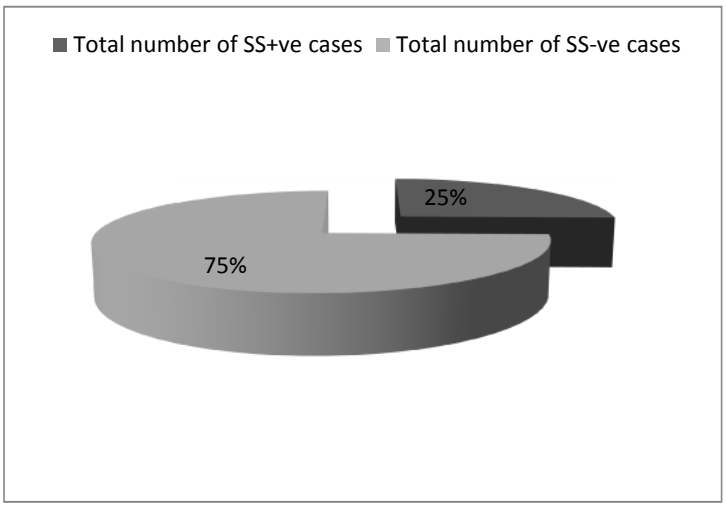


Figure 1

Out of 18 SS positive cases, 3(16.7%) were having primary SS and remaining 15(83.3%) had secondary SS.

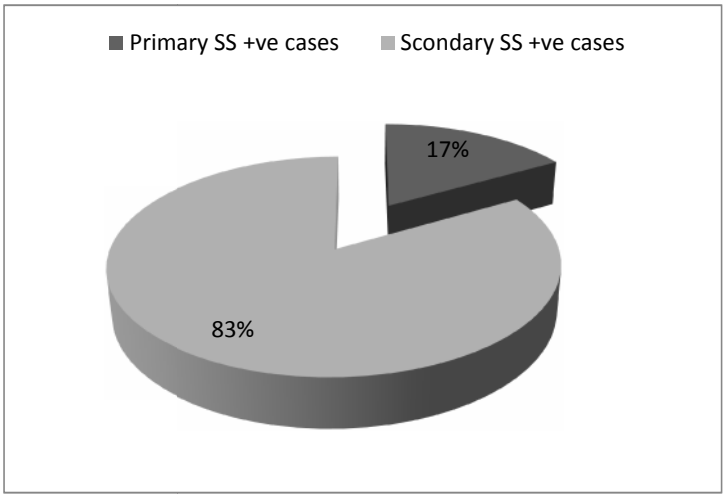


Figure 2

Gender distribution in provisional SS cases is illustrated in table 1 (below). All SS positive cases were females and no male was diagnosed SS positive.

	Male	Female
SS +ve	0	18
SS –ve	5	48
Total	**5**	**66**

Table 1

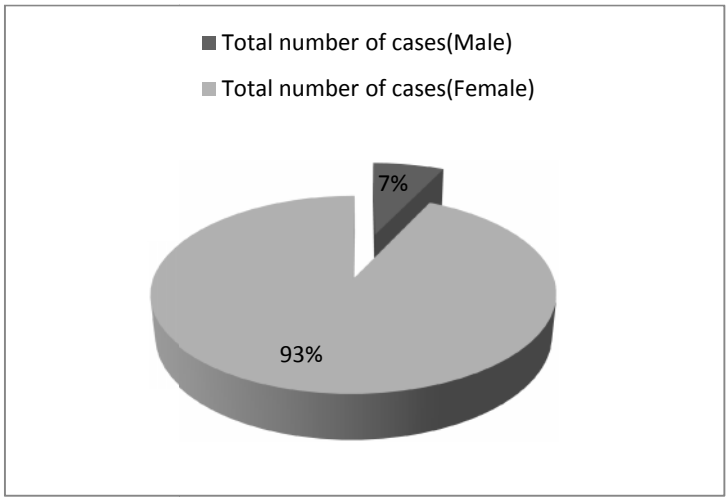


Figure 3

Gender distribution in SS positive cases

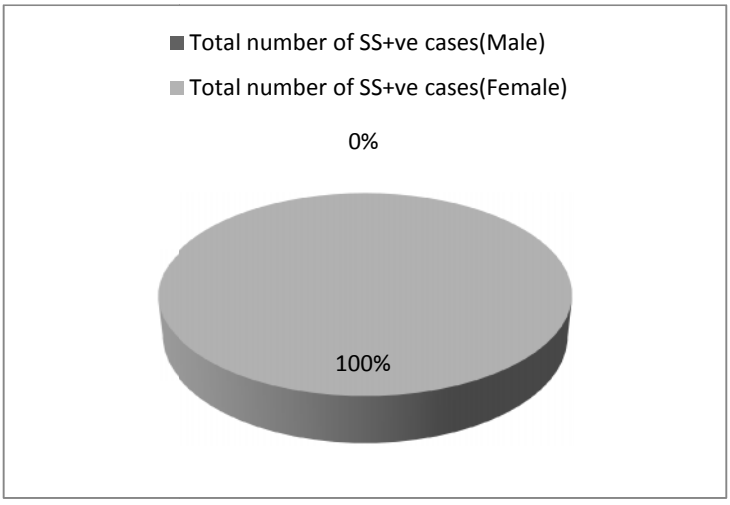


Figure 4

Table below list the distribution of total cases diagnosed in various age groups.

		No of cases		
		SS -ve cases	**SS +ve cases**	**Total**
Age group	**0-10**	0	0	0
	11-20	0	0	0
	21-30	13	2	15
	31-40	11	4	15
	41-50	20	5	25
	51-60	8	5	13
	61-70	1	2	3
Total		**53**	**18**	**71**

Table 2

Of total 71 cases, Xerostomia was positive in 54 cases and negative in 17. Of 54 Xerostomia positive cases, 18 were found SS positive. There was no case of SS without Xerostomia. Table 2(below) summarizes the occurrence of Xerostomia and USWF in total number of cases.

		Xerostomia (occurrence in all cases)	
		+ve	-ve
USWF	+ve	27	0
	-ve	27	17

Table 3

Table 4(below) summarizes the occurrence of Xerostomia and USWF in SS positive cases and SS negative cases.

		Xerostomia occurrences			
		SS +ve cases		SS –ve cases	
		+ve	-ve	+ve	-ve
USWF	+ve	18	0	9	0
	-ve	0	0	27	17

Table 4

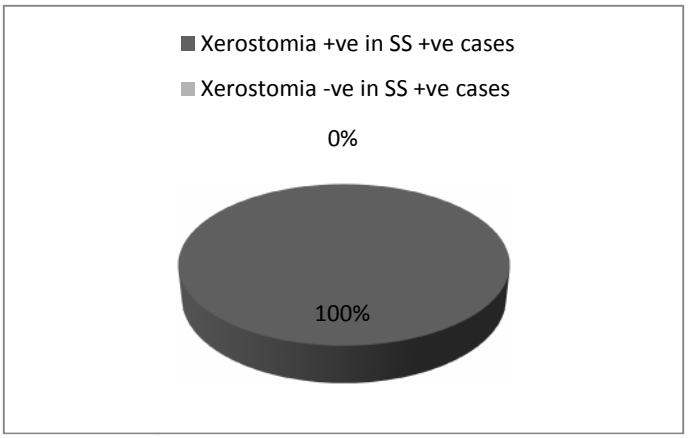


Figure 5

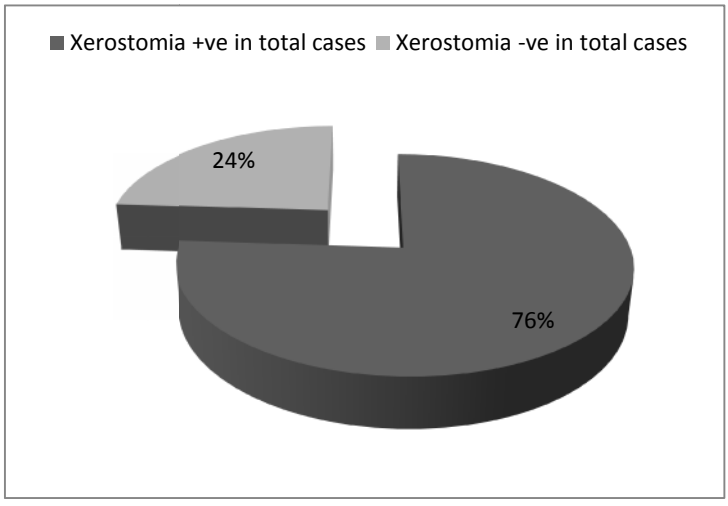


Figure 6

A closer look at Xerostomia and USWF occurrences inferred that presence of Xerostomia and USWF together increases the probability of SS occurrence.

As illustrated in figure 4 below, 33.3% of Xerostomia positive cases, 54.8% of KCS positive cases , 66.7% of USWF positive cases and 83.3% of ScT-1 positive cases were found SS positive cases. So it can be inferred that there is close correlation between positive ScT-1 test and occurrence of SS.

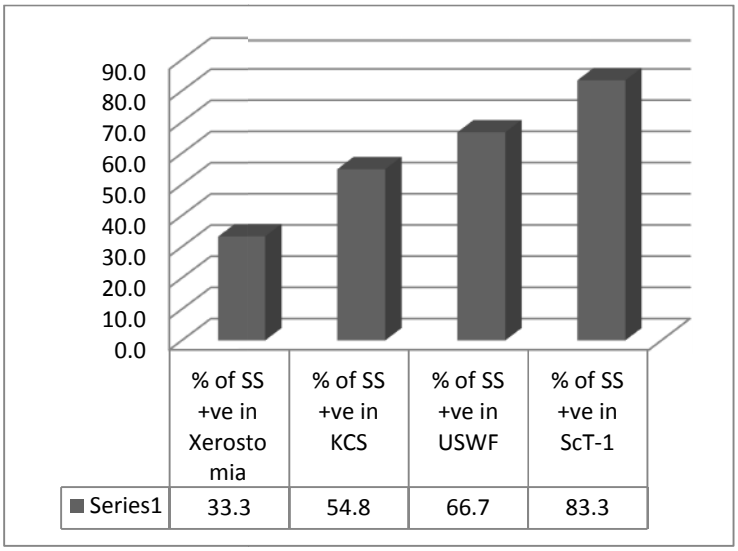


Figure 7

Figure 5 below shows the occurrence of positive KCS in total cases and SS positive and SS-ve cases respectively.

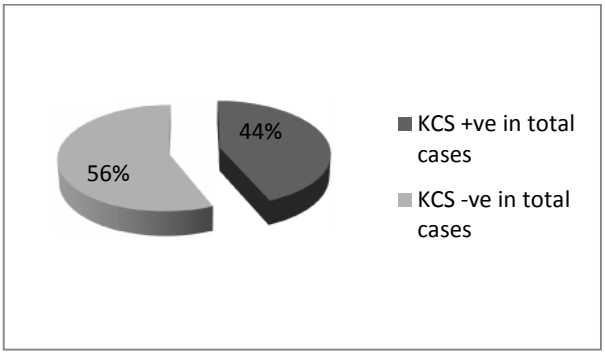


Figure 8

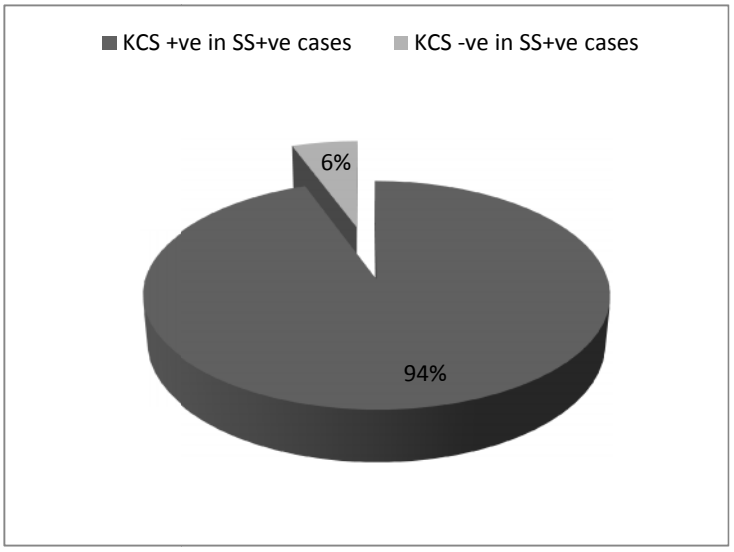


Figure 9

Histopathological results

Of total 71 cases, 34/71 (47.9%) showed acinar degeneration and 37/71 (43.7%) were free from acinar degeneration. In 10 cases of SS, AD was present whereas it was present in 24 SS-ve cases. AD was not found in 8 SS +ve cases and 29 SS –ve cases.

ACINAR DEGERATION IN ALL CASES

		AD	
		Present	**Absent**
SS	**Present**	10	8
	Absent	24	29
Total cases		**34**	**37**

Table 5

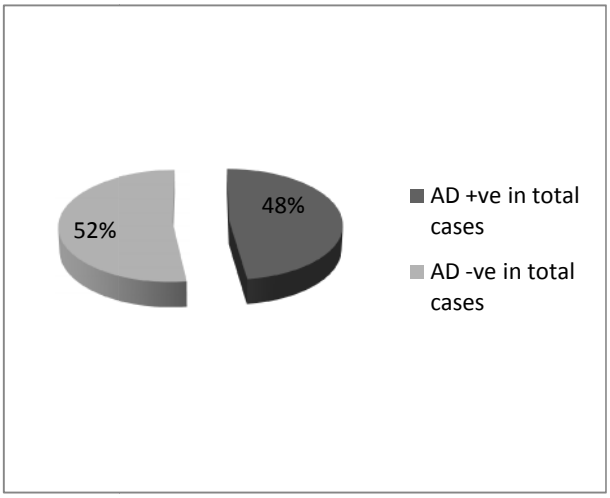


Figure 10

DISTRIBUTION OF DUCTAL PROLIFERATION, DUCTAL ECTASIA AND FOCAL INFLAMMATION

		DP		DE		FI	
		Present	Absent	Present	Absent	Present	Absent
SS	Present	8	10	1	17	10	8
	Absent	27	26	4	49	8	45
Total cases		**35**	**36**	**5**	**66**	**18**	**53**
		Figure 11		**Figure 12**		**Figure 13**	

Table 6

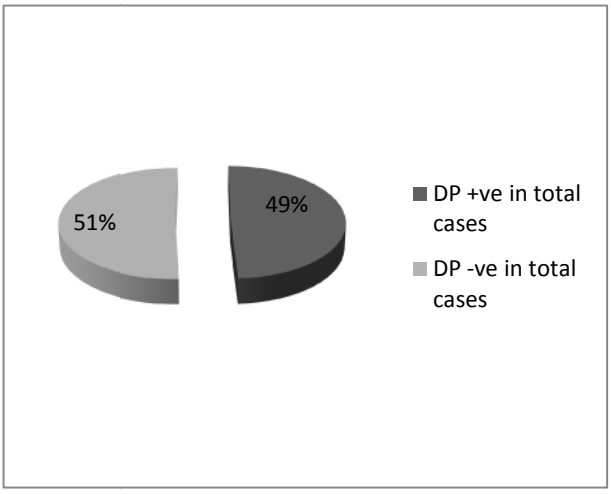


Figure 11

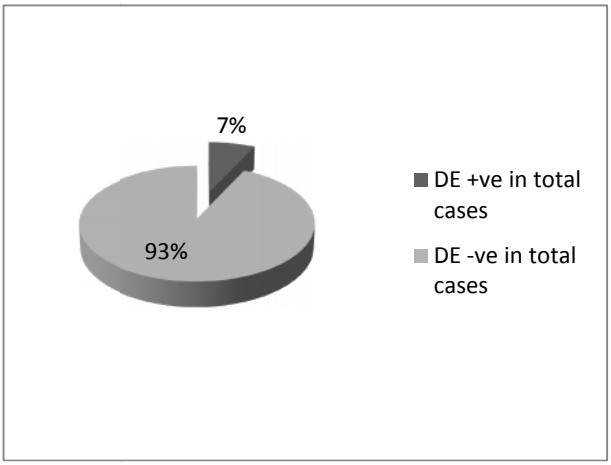


Figure 12

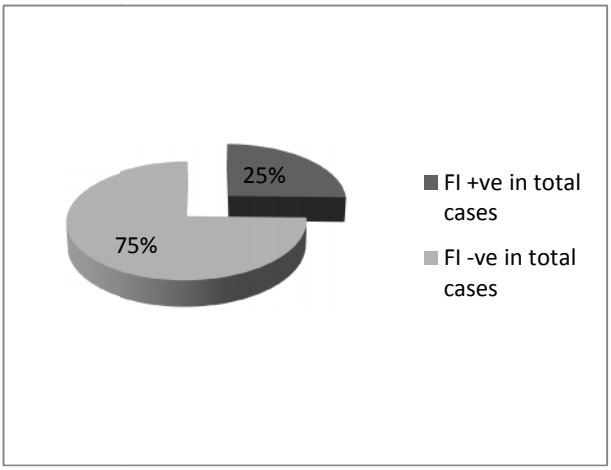


Figure 13

Scattered Inflammation, Interstitial Fibrosis and Adipose Tissue

		SI		IF		AT	
		Present	**Absent**	**Present**	**Absent**	**Present**	**Absent**
SS	**Present**	13	5	7	11	5	13
	Absent	23	30	19	34	12	41
Total cases		**36**	**35**	**26**	**45**	**17**	**54**

Table 7

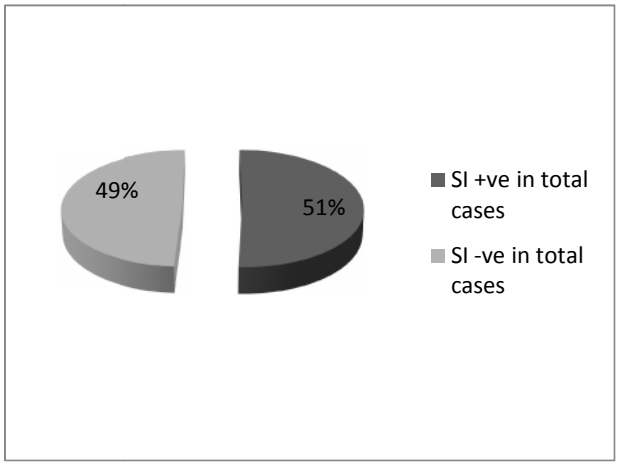


Figure 14

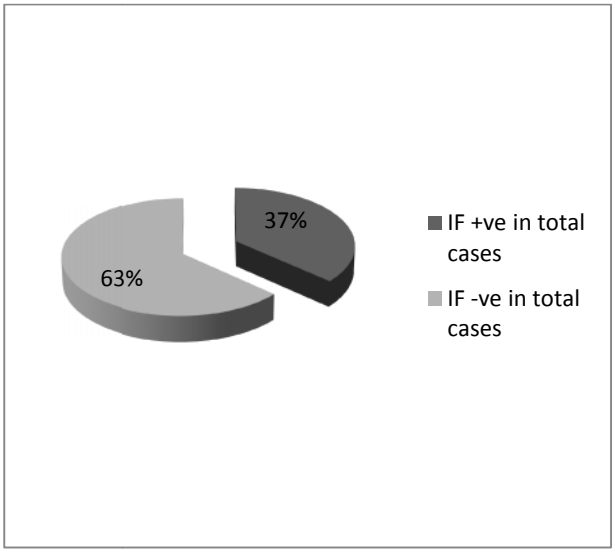


Figure 15

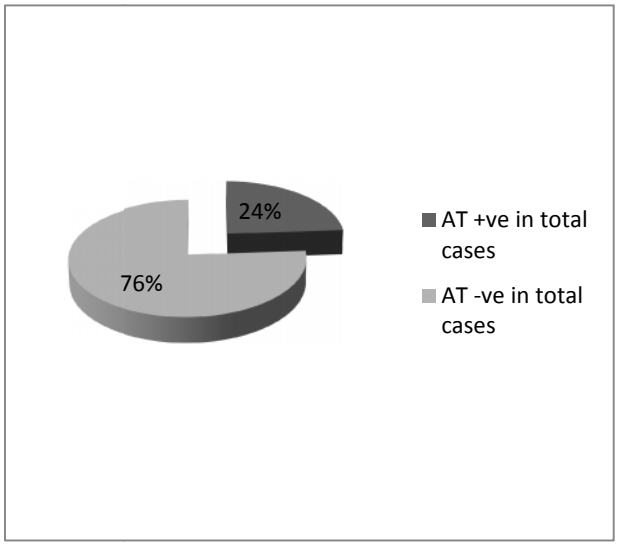


Figure 16

Figure below is snapshot of observed histopathological occurrences in total cases

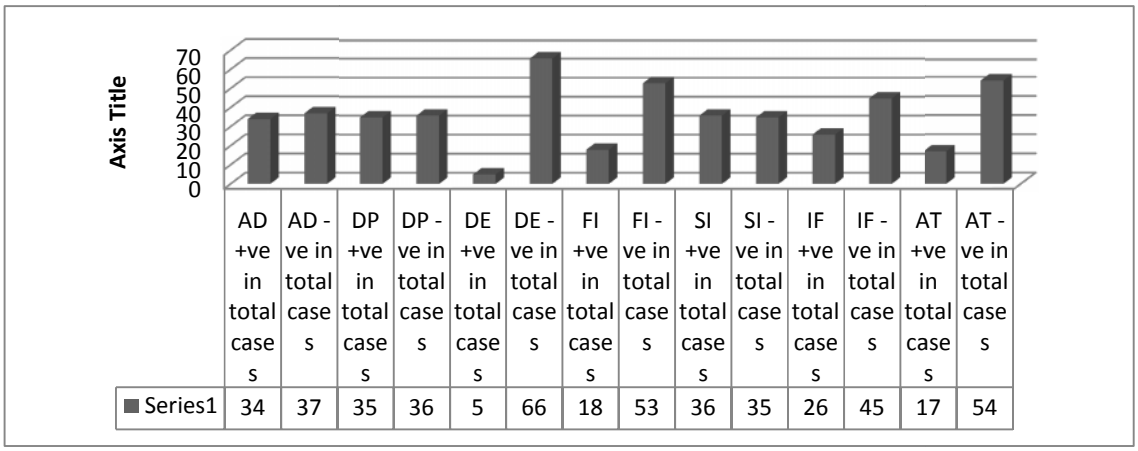


Figure 17

Distribution of Vascularity observed in the both the groups are plotted in figure 18 (below)

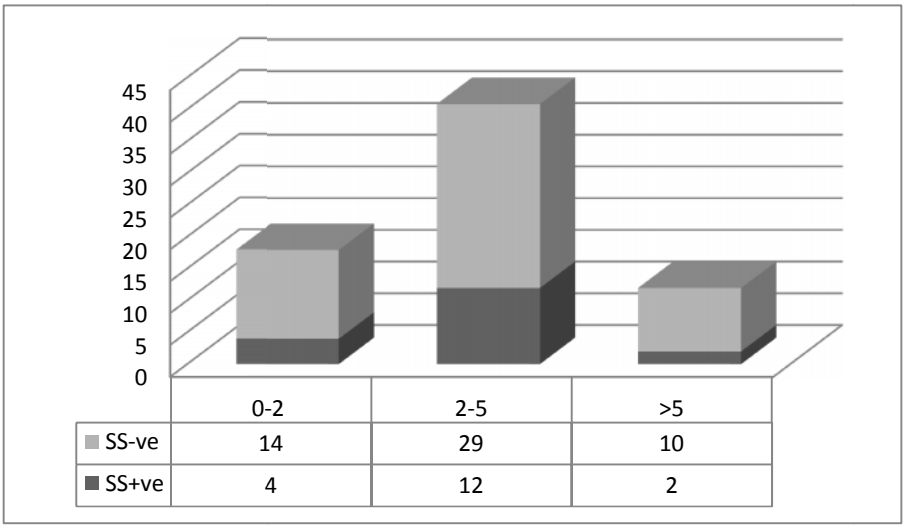


Figure 18

Vascularity distribution in total 71 cases is tabulated in table below and ploted in figure 20 (below)

	0-2	2-5	>5
Total cases	18	41	12
Total cases (%)	25.4	57.7	16.9

Table 8

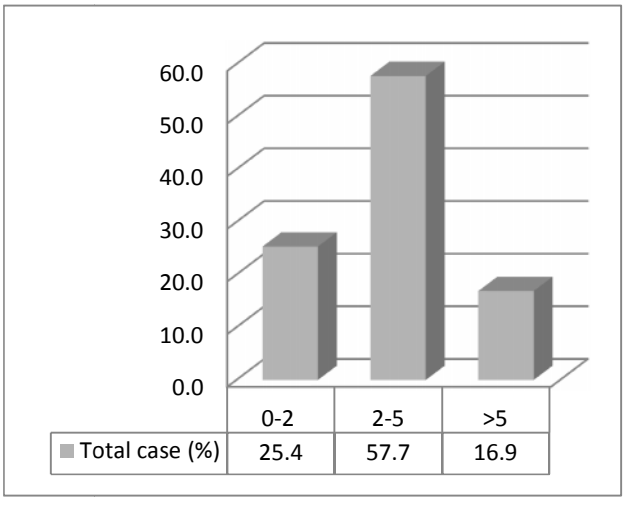
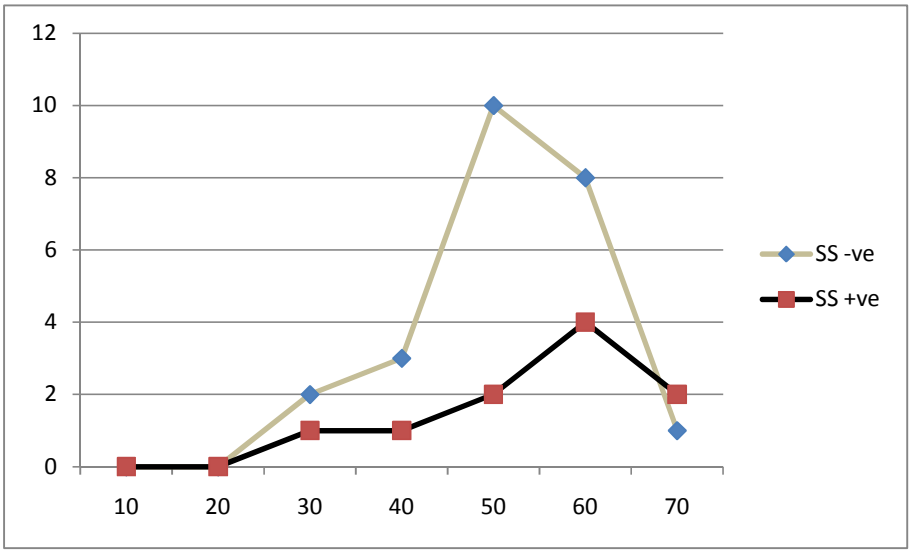


Figure 19



Distribution of Acinar degenrationin relation to age.

Discussion

Discussion

From 1 Jan 2009 to 30 Jul 2009, 84 cases with the provisional diagnosis of SS presented to the department of Oral Pathology, out of which only 71 cases were taken into consideration due to lack of data for rest of the cases.

18 cases were diagnosed as SS which constituted 25.4% of the total cases under study. Of these, 3 cases were of primary SS and 15 cases were of secondary SS. Primary SS cases occupied 16.7% of the SS cases and 4.2% of total study cases. Secondary SS cases were more than Primary SS syndrome and were around 83.3% of SS cases and 21.1% of total cases. The ratio of occurrence of primary SS to secondary SS was 1:5.

GENDER DISTRIBUTION

Female constituted 93% of sample size and males 7%. So, the ratio of female to male in total sample of provisional SS cases was 13.2:1.

In SS positive cases all the 18 patients were female and none of the male patients was found SS positive. The ratio of female to male in SS positive cases ranged from 9:1 to as high as 24:1. [8-10]As no male was affected so our male to female ratio comes out to be more than the highest reported ratio. But our sample size was small and serological factor was not taken into consideration so there are chances that with all the required investigations we could have got a more predictive data and preponderance of the gender in this study.

48 female patients (90.6%) and 5 male (9.4%) comprised the SS negative group. So the female to male ratio was 9.6:1 which is significantly lower than the proportion of female patients affected in relation to male in SS+ve group in the present study, but is similar to the usual ratio of female to male patients affected with SS. [8-10]

AGE

The age of the patients reported ranged from 3rd decade till 7th decade with a mean of 42.3±11 yrs.

Mean age of females was 42.2 yrs. Mean age of male was 43.4 yrs.

No case in the 1st and 2nd decade reported with the complaint. This is in accordance to the usual age group which is affected by connective tissue disease mainly rheumatoid arthritis. Though Sjogren's syndrome can affect any age but most commonly occurs in 4th and 5th decade of life. So the present study group matches with the literature.[1]

The age of the patients affected with SS ranged from 3rd to 7th decade with mean age of 45.4±11.4 yrs.

Mean age of secondary SS cases was 46.1 yrs and of primary SS cases was 42 yrs.

SS negative cases also spanned from 3rd decade till 7th decade with mean age of 42.9±10.8 yrs.

Mean age of males was 43.4 yrs and that of females was 41.1 yrs in SS-ve cases.

Mean age of SS positive cases was higher than SS negative cases and total cases. This is in accordance with the literature which states that the patients which are affected with the syndrome are generally older than the patients of connective tissue disease. As this is a slowly progressing condition and diagnostic delay is present due to wide spread spectrum of systemic manifestation, is usually diagnosed later than the other diseases. Also patients suffering from primary SS are usually younger than the secondary SS cases, though in the present study the number of primary SS cases are very less to give a more significant age predilection but still it can be inferred that it tends to occur in slightly younger patients than those who manifest connective tissue along with it. Mean age of SS negative cases was slightly higher though not significant than the mean age of total sample. The cases of SS+ve were older than the case of SS-ve as it is an insidious condition and will show its sign and symptom

slightly late in life and thus the present age group predilection is in accordance with the literature.

There was no case below 2nd decade with the complaints. 25/71(35.2%) cases among all belonged to 5th decade. 15(21.1%) cases were in 3rd and 4th decade. The number slightly decreased in 6th decade to 13(18.3%) and only 3(4%) cases were of 7th decade.

Cases of SS showed a gradual increase in frequency with the age which lowers down in the oldest group [2/18(11.1%) in 4th, 4/18(22.2%) in 5th, 5/18(27.8%) in 6th and 2/18(11.1%) in 7th decade]. So most of the patients were affected in middle and old age group that is 4th to 6th decade, which is in accordance with other studies which showed middle aged women to be most affected with SS.

In SS-ve group 13/53(24.5%) cases were young belonging to 3rd decade then there was a slight fall in the frequency in the next decade to 11/53(20.7%) and a sudden rise in fifth decade to 20/53(37.7%), again there was a decrease in frequency7/53(15.1%) as age increased to 6th decade to as low as 1/53(1.9%) in 7th decade. This pattern was not correlating to the pattern of frequency in SS+ve cases rather correlated well to the total number of cases.

Oral Component

54/71(76%) responded positively for the symptoms of dry mouth or xerostomia and out of these xerostomic patients 18/54(33.3%) were diagnosed as SS+ve cases. None of the patients who denied the presence of xerostomia symptoms had SS. All (100%) the cases of SS showed symptoms of xerostomia. Almost 2/3rd of the patient complained of dry mouth, this is due to referral of patients with rheumatoid arthritis with dry mouth, despite of this selection bias only 1/3 of the cases

went for SS positivity. This means that the predictability of xerostomia for the possibility of patients to SS case is significant. This can be due to various causes. As there is decrease in the salivary flow as the age increases so more patients in older age group complained of dry mouth. Most common cause of dry mouth is side-effects of the drugs. Patients who are suffering from connective tissue diseases are on drugs for long time, this may also affect secretion of saliva and more patients complain of xerostomia.

Out of 53 cases of SS-ve cases 36/53(67.9%) reported dry mouth symptoms. Rest 17/53(32.1%) denied any such symptom. So, in SS-ve cases the number of patients reporting dryness was almost twice than the cases which didn't feel any oral dryness. About 2/3rd of the cases responding positively for xerostomia in total cases were SS-ve.

So, xerostomia is not a reliable symptom in predicting the probability of SS as only 1/3rd cases of xerostomia were diagnosed as SS.

The objective test to confirm the presence of xerostomia is done by calculating the Unstimulated Whole Salivary Flow (UWSF). 54 cases complained of dry mouth but only 27/54 (50 %) of cases the test was positive rest were negative on test. The test was not positive for any of the patient without complaint of dry mouth.

In all the 18 cases of SS, dry mouth was present along with the decrease in unstimulated whole salivary flow. None of the case showed any discrepancy between the symptom and the objective test. This can very well be possible due to selection bias. As serological factor remained the major criteria; along with the minor criteria it was used to diagnose the cases of SS. But in 90% of the cases this investigation result was not available, so more stress was kept on these minor criteria and they showed higher prevalence in SS+ve cases and thus showed selection bias.

In 53 cases of SS-ve, only 9 (17%) cases showed both the subjective symptom and objective sign of xerostomia. 27(51%) cases showed discrepancy between the subjective symptom and the objective test. In addition, no case denying the dry mouth symptom showed decreased whole salivary flow rate.

In contrast to SS+ve cases where not even a single case showed discrepancy between symptom and sign, almost 2/3rd cases of SS-ve group showed this mismatch between dry mouth symptom and objective test.

As compared to the cases affected with SS+ve , only 1/3 of the SS-ve cases confirmed the symptom. The sensitivity and specificity of the USWF test was 1,

0.83. respectively.

Positive predictive and the negative predictive values 0.67, 1. respectively.

Combined effect of symptom and objective sign significantly improved the probability of predicting the possibility of SS.

Ocular Component

31 out of total cases (43.7%) complained troublesome eyes and were considered positive for the subjective symptom of dry eyes or Keratoconjunctivitis Sicca (KCS). 57.3% (40/71) did not complained of dry eyes. So, the ratio of positive symptoms to negative symptoms of KCS was 0.77:1.

Less number of patients complained for dry eyes when compared to the number of cases complaining dry mouth.

Out of 18 SS+ve cases 17(94.4%) showed KCS and only one patient didn't complain of dry eyes. So, the ratio of cases with and without KCS symptom was 17:1.

14 cases of 53 (26.4%) SS-ve were symptomatic for dry eyes and 39 (73.6%) cases were asymptomatic. So, the ratio of symptomatic to asymptomatic cases with SS-ve diagnosis was 0.36:1.

More than 50 % of cases complaining of KCS were ultimately diagnosed as SS. This was in contrast to the xerostomia symptom, though less number of patients were affected by dry eyes but the patient in SS-ve group were less as compared to the greater number of patients complaining xerostomia in SS-ve group. Positivity of KCS was significantly higher in SS+ve cases when compared to SS-ve cases. Specificity of this symptom was greater than the xerostomia. KCS has higher predictability than xerostomia in predicting the possibility of SS.

33/71(46%) cases out of total sample were symptomatic for KCS. Out of these 20 (60.6%) cases showed ScT-1 test positivity but 11 (39.4%) cases couldn't qualify this test and failed to show decreased lacrimal flow.

Specificity and sensitivity of the Schirmer's test was 0.83, 0.95 respectively.

Predictive value of KCS was high as compared to the xerostomia.

Histological Features

Acinar Degeneration

34/71 case showed acinar degeneration and 37/71 cases didn't show this feature. So, half of the sample showed acinar degeneration. But, when we compared the number of cases affected in individual groups, 10/18 cases showed acinar degeneration compared to 24 /53 in SS-ve group. Though it looks as more number of cases showed acinar degeneration in SS-ve group but due to unequal sample size the percentage of the cases showing the degenerative feature was calculated from their respective sample size. More than 50 % of the cases from SS +ve group were having

degenerative process when compared to SS-ve group which shared only 30% of its sample size.

Ductal proliferation

About 50% of the total sample showed ductal proliferation and the picture was same as in acinar degeneration. As in the case of acinar degeneration, ductal proliferation was seen in about 44% cases of SS+ve and affected only 33% cases of SS-ve group. Till this, it seems that acinar degeneration and ductal proliferation go hand in hand and affects greater cases of SS+ve group than SS-ve group.

Ductal Ectasia

Only 5 cases out of 71 case showed this feature comprising 7% of the sample size.

Only 1/18 case showed this degenerative process comprised of 5.6% of SS+ve sample. Rest 4 cases were from SS-ve group comprising 4.9% of the SS-ve sample.

So, actual number of cases showing ductal ectasia were not significant in both the samples and the figures were too low to be compared of. Still, almost same share of the cases were affected leaving us to conclude that ductal ectasia is a non specific feature which can be present in either of the group.

So, contrary to the belief that minor salivary gland of SS+ve cases shows less degenerative features, [20] this study showed that almost half of the sample size of SS+ve cases had degenerative processes. This is in accordance to Chisholm[62] who said that degenerative features can be seen in SS+ve cases.

Interstitial Fibrosis

In 26/71 cases interstitial fibrosis was noted which comprised of 36.6% of sample size. Out of this, 19 cases were from SS-ve group and 7 cases were from SS+ve group. Though it appears that 73% of the share of interstitial fibrosis was

shared by SS-ve group and SS+ve group constituted only 27%, but the sample size for SS-ve group was about three times larger. Keeping that in mind the ratio of cases of interstitial fibrosis of SS-ve group and SS+ve group was calculated that was in accordance to the sample size. So, almost equal number of the cases showed interstitial fibrosis.

When the number of cases were observed according to their respective sample size it was observed that almost equal percentage of cases showed fibrosis, thereby making it a non specific feature when comparing SS+ve cases and SS-ve cases.

Adipose tissue

It was present only in 17/71 (24%) cases and the number of cases from both the groups were equally affected. So, presence of adipose tissue as a histological feature was not specific with respect to comparison of both the groups.

Vascularity

Number of vessels in minor salivary gland lobule was counted in all the cases in high power field. Around 57.7% of the total sample showed moderate vascularity, one quarter of the cases showed minimal vascularity and less than a quarter(16.9%) showed high vascularity. The same pattern was seen in both the groups. In both the groups around 50-60% cases belonged to moderate vascularity.

Around 2/3rd of SS+ve cases had moderate vascularity when compared with SS-ve group in which slightly more than half comprised of moderate vascularity, but the difference was not significant to arrive at any specific conclusion.

Scattered Inflammation

Around half of the total cases showed scattered inflammatory infiltrate. Surprisingly, around 72% of the cases of SS+ve cases showed scattered inflammation when compared to the SS-ve group which shared only 43.4% from their respective groups.

Focal Inflammation

Only 25% of the total sample showed foci of inflammatory cells out of which 10 cases were diagnosed as SS+ve cases and rest 8 were SS-ve cases. This was vey surprising because focal inflammation has a good balance of specificity and sensitivity but in this study it got reduced to slightly more than 50%. This can be due to the unavailability of the serological investigations, which would have been there could have transformed probable SS cases in to SS+ve cases and thus could have increased the specificity of the focal inflammation which is considered to be characteristic of SS+ve cases.

None of the cases showed Epimyoepithelial islands and Squamous metaplasia which is frequently seen in the major salivary gland of SS+ve cases. Only one case of SS+ve showed germinal center formation. One of the cases from SS-ve group showed giant cells but when examined systemically no pathology was found except joint pains.

Acinar degeneration was found to be increasing with age. This pattern was followed by both the groups though the peak in SS+ve was found at an older age when compared to the SS-ve group.

So, it can be inferred that acinar degeneration is an aging process which can be found in SS+ve cases affecting the older age group.

Comparison of the histological and clinical findings in cases of SS+ve cases.

18 cases constituted the SS+ve group, out of these all 18 cases complained xerostomia with 17 cases showing positive objective result.

Acinar degeneration and ductal proliferation was found in around half of the cases presenting with xerostomia and keratoconjunctivitis sicca. Though 72 % cases showed scattered inflammation but other degenerative features were found in less than 1/3rd cases.

One thing was notable that an increased number of foci was present in SS+ve cases than SS-ve cases.

SS-ve group

36 cases complained of dry mouth out of them 20 showed acinar degeneration and 15 cases showed ductal proliferation, 23 showed scattered inflammation.

So, a better correlation was found between clinical features in SS-ve group than SS+ve group in relation to histological features.

Summary and Conclusion

Summary

About 25% cases having provisional Sjogren syndrome were diagnosed as definite Sjogren's syndrome positive. Sjogren's syndrome affected older age group and showed characteristic female predilection compared to non-Sjogren's cases. Clinical features of xerostomia and keratoconjuctivitis sicca were seen in both Sjogren's syndrome positive and negative cases with more expression in Sjogren's syndrome cases. Both showed degenerative changes on histopathological evaluation of minor salivary glands but a better correlation was found between clinical and histological features in non Sjogren's cases when compared to Sjogren's syndrome cases

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Conclusion:

Correlation was found between histological and clinical features in Sjogren's syndrome, but it was not consistently present in all the cases. Hence diagnosis of Sjogren's syndrome should be rendered carefully after observing clinical features and histological features.

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Annexure

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PROFORMA

Name:
Age:
Gender:
Date:
Dental OP No:
Histopathology No:

GGH OP No & Date:
RCC No & Date:

Chief Complaint:

Ocular symptoms

1. Have you had daily, persistent, troublesome dry eyes for more than 3 months?
2. Do you have recurrent sensation of sand or gravel in the eyes?
3. Do you use a tear substitute more than 3 times a day?

Oral symptoms

4. Have you had a daily feeling of dry mouth for more than 3 months?
5. Have you had recurrently or persistently swollen salivary gland as an adult?
6. Do you frequently drink liquid to aid in swallowing dry foods?

Schirmer's test
Unstimulated whole salivary flow

History of present illness

History of past illness

ASSOCIATED CONNECTIVE TISSUE DISEASE

Rheumatoid Arthritis
Systemic Lupus Erythematosus
Polyarthritis Nodosa
Polymyositis
Scleroderma

ANY OTHER ASSOCIATED DISEASE
Kidney involvement
Lung involvement
Liver involvement
CNS disorder
Thyroid
Diabetes
Hypertension

LAB INVESTIGATIONS
Hb
ESR
TLC
DLC
RF
CRP
SSA
SSB

HISTORY OF MEDICATIONS

Any other relevant information/notes

Department of Oral Pathology
Tamil Nadu Government Dental College & Hospital
Chennai 600 003

Informed Consent Form in English

(A copy of Tamil transcript will be provided to the patient).

Study Title: **The concordance of minor salivary gland histology with clinical parameters in patients with a provisional diagnosis of Sjogren's syndrome**.

Name: O.P. No

Address: Code No

I,…… aged……, exercising my free power of choice, hereby give my consent to be included as a participant in the study.

I agree to the following:

- I have been informed to my satisfaction about the purpose of the study and study procedures.
- I agree to cooperate fully and also agree to report to my doctor for a regular follow up as and when required for research.
- I have informed my doctor about all the medications that I am currently taking and other systemic diseases that I am afflicted with.
- I herby give permission to use my medical records for research purpose. I am told that investigating doctor and the institution will keep my identity confidential.

Name of the participant Signature/Thumb impression
Date

Name of the investigator Signature
Date

S. No.	HP: No.	Age (Yrs)	Gender	Ocular symptoms	Oral symptoms	Schirmer's test (mm/5min)	USWF (ml/15 min)	Histopathology	Serology	SS	CT Disease
1	12321	50	F	Absent	Present	>5	>1.5	NC	ND	Absent	Absent
2	12322	40	M	Absent	Absent	>5	>1.5	NC	ND	Absent	Absent
3	12323	30	F	Absent	Absent	>5	>1.5	C	ND	Absent	Absent
4	12327	45	F	Absent	Present	>5	>1.5	NC	ND	Absent	Present
5	12337	48	F	Absent	Absent	>5	>1.5	NC	ND	Absent	Present
6	12338	36	F	Present	Present	**<5**	<1.5	NC	ND	Present	Present
7	12344	25	F	Present	Present	>5	1.5	C	ND	Present	Present
8	12347	42	F	Present	Present	>5	>1.5	NC	ND	Absent	Absent
9	12350	57	F	Absent	Present	>5	>1.5	NC	ND	Absent	Absent
10	12352	65	F	Absent	Present	**5**	>1.5	NC	Negative	Absent	Absent
11	12354	45	F	Present	Present	**5**	<1.5	NC	ND	Present	Present
12	12364	47	F	Present	Present	>5	>1.5	C	ND	Absent	Present
13	12373	47	F	Present	Present	<5	<1.5	NC	Present	Present	Absent
14	12374	47	F	Present	Present	**5**	>1.5	NC	Negative	Absent	Present
15	12375	40	F	Absent	Present	>5	>1.5	NC	ND	Absent	Present
16	12378	35	F	Present	Present	**<5**	<1.5	C	ND	Present	Present
17	12381	50	F	Present	Present	>5	>1.5	NC	ND	Absent	Present
18	12383	47	F	Present	Present	>5	1.5	C	ND	Present	Absent
19	12401	55	F	Present	Present	5	<1.5	NC	ND	Absent	Absent
20	12403	40	F	Absent	Absent	>5	>1.5	NC	ND	Absent	Present
21	12408	55	F	Absent	Present	>5	<1.5	NC	ND	Absent	Present
22	12410	39	F	Absent	Present	>5	<1.5	NC	Negative	Absent	Absent
23	12413	46	M	Present	Present	<5	<1.5	NC	Negative	Absent	Absent
24	12415	55	F	Present	Present	>5	>1.5	NC	ND	Absent	Present
25	12436	52	F	Present	Present	5	1.5	NC	Negative	Present	Present
26	12438	40	F	Absent	Present	<5	>1.5	NC	Negative	Absent	Present
27	12444	35	F	Absent	Absent	5	>1.5	NC	ND	Absent	Present
28	12449	45	F	Absent	Present	>5	>1.5	NC	ND	Absent	Absent
29	12456	30	F	Absent	Present	>5	>1.5	NC	ND	Absent	Present
30	12462	32	F	Present	Present	5	1.5	NC	Present	Present	Absent
31	12466	49	F	Present	Present	>5	>1.5	C	ND	Absent	Absent
32	12472	27	F	Absent	Present	>5	>1.5	NC	ND	Absent	Present
33	12479	42	F	Absent	Present	5	>1.5	NC	ND	Absent	Present
34	12481	30	F	Absent	Present	>5	<1.5	C	ND	Present	Present
35	12483	61	F	Present	Present	<5	1.5	NC	ND	Present	Present
36	12493	23	F	Absent	Absent	>5	>1.5	NC	ND	Absent	Present
37	12502	54	F	Absent	Absent	>5	>1.5	NC	ND	Absent	Present
38	12504	21	F	Absent	Absent	>5	>1.5	NC	ND	Absent	Present
39	12507	22	F	Absent	Absent	>5	>1.5	NC	ND	Absent	Present

40	12519	55	F	Absent	Absent	>5	>1.5	NC	ND	Absent	Absent
41	12521	42	F	Absent	Present	<5	>1.5	NC	ND	Absent	Absent
42	12533	45	F	Absent	Present	>5	<1.5	NC	ND	Absent	Present
43	12538	55	F	Present	Present	<5	<1.5	NC	Present	Present	Present
44	12551	42	F	Absent	Present	>5	>1.5	NC	ND	Absent	Present
45	12553	30	F	Absent	Present	>5	<1.5	NC	ND	Absent	Present
46	12566	40	F	Absent	Absent	>5	>1.5	NC	ND	Absent	Present
47	12580	49	F	Present	Present	>5	1.5	NC	ND	Absent	Present
48	12582	50	F	Absent	Present	>5	>1.5	NC	ND	Absent	Present
49	12586	41	F	Present	Present	<5	1.5	C	ND	Present	Present
50	12588	29	M	Absent	Present	>5	>1.5	NC	ND	Absent	Absent
51	12605	55	F	Present	Present	>5	<1.5	NC	ND	Absent	Present
52	12608	52	F	Present	Present	5	<1.5	NC	ND	Present	Present
53	12612	36	F	Present	Present	<5	<1.5	C	ND	Present	Present
54	12615	29	F	Absent	Absent	>5	>1.5	NC	Negative	Absent	Absent
55	12629	24	F	Absent	Present	>5	>1.5	NC	ND	Absent	Present
56	12631	32	F	Present	Present	>5	>1.5	NC	ND	Absent	Present
57	12632	25	F	Absent	Absent	>5	>1.5	NC	ND	Absent	Present
58	12643	47	F	Present	Present	<5	>1.5	NC	ND	Absent	Absent
59	12646	32	F	Present	Absent	>5	>1.5	NC	ND	Absent	Present
60	12654	36	F	Absent	Absent	>5	>1.5	NC	ND	Absent	Present
61	12656	46	F	Absent	Absent	5	>1.5	C	ND	Absent	Present
62	12657	67	F	Present	Present	<5	<1.5	C	ND	Present	Present
63	12663	42	M	Absent	Present	>5	<1.5	NC	ND	Absent	Present
64	12666	40	F	Present	Present	<5	>1.5	NC	ND	Absent	Absent
65	12670	43	F	Absent	Present	5	>1.5	NC	ND	Absent	Present
66	12672	28	F	Absent	Absent	>5	>1.5	NC	ND	Absent	Present
67	12676	28	F	Absent	Present	>5	>1.5	NC	ND	Absent	Absent
68	12678	47	F	Present	Present	<5	<1.5	C	ND	Present	Present
69	12681	55	F	Present	Present	<5	1.5	NC	ND	Present	Present
70	12684	60	M	Absent	Present	>5	>1.5	NC	ND	Absent	Present
71	12707	55	F	Present	Present	<5	<1.5	NC	ND	Present	Present

S. No.	HP: No.	Age (Yrs)	Sex	HP	Apparently Normal	Acinar Degeneration	Ductal Proliferation	Ductal Ectasia	Inflammatory Infiltrate	Focal	Scattered	Interstitial Fibrosis	Vascular Component (HPF)	Adipose Tissue	Germinal Centre Formation	Giant Cells	Squamous metaplasia	Epimyoepithelial islands	SS
1	12321	50	F	NC	Absent	Present	Present	Absent	Present	Absent	Present	Absent	0.8	Absent	Absent	Absent	Absent	Absent	Absent
2	12322	40	M	NC	Absent	Present	Present	Present	Absent	Absent	Absent	Present	6.5	Absent	Absent	Absent	Absent	Absent	Absent
3	12323	30	F	C	Absent	Present	Present	Absent	Present	Present(2f)	Present	Present	6.2	Absent	Absent	Absent	Absent	Absent	Absent
4	12327	45	F	NC	Present	Present	Present	Absent	Present	Present(<1f)	Present	Present	2.0	Present	Absent	Absent	Absent	Absent	Absent
5	12337	48	F	NC	Present	Absent	Present	Absent	Present	Absent	Present	Absent	4.8	Absent	Absent	Absent	Absent	Absent	Absent
6	12338	36	F	NC	Present	Absent	Absent	Absent	Absent	Absent	Absent	Absent	1.0	Absent	Absent	Absent	Absent	Absent	Present
7	12344	25	F	C	Absent	Present	Present	Absent	Present	Present(5f)	Present	Present	1.0	Absent	Absent	Absent	Absent	Absent	Present
8	12347	42	F	NC	Present	Absent	Absent	Absent	Present	Present(<1f)	Absent	Absent	4.8	Absent	Absent	Absent	Absent	Absent	Absent
9	12350	57	F	NC	Absent	Present	Present	Absent	Absent	Absent	Absent	Absent	4.7	Present	Absent	Absent	Absent	Absent	Absent
10	12352	65	F	NC	Absent	Present	Present	Absent	Present	Absent	Present	Present	2.8	Absent	Absent	Absent	Absent	Absent	Absent
11	12354	45	F	NC	Present	Absent	Absent	Absent	Absent	Absent	Absent	Absent	0.5	Absent	Absent	Absent	Absent	Absent	Present
12	12364	47	F	C	Present	Absent	Absent	Absent	Present	Present(1f)	Absent	Absent	1.9	Absent	Absent	Absent	Absent	Absent	Absent
13	12373	47	F	NC	Absent	Present	Present	Absent	Present	Absent	Present	Absent	3.7	Present	Absent	Absent	Absent	Absent	Present
14	12374	47	F	NC	Present	Present	Present	Absent	Present	Present(<1f)	Present	Absent	1.6	Present	Absent	Absent	Absent	Absent	Absent
15	12375	40	F	NC	Present	Present	Present	Absent	Absent	Absent	Absent	Absent	0.9	Present	Absent	Absent	Absent	Absent	Absent
16	12378	35	F	C	Present	Absent	Absent	Absent	Present	Present(3f)	Present	Absent	4.2	Absent	Present	Absent	Absent	Absent	Present
17	12381	50	F	NC	Present	Absent	Present	Absent	Absent	Absent	Absent	Absent	4.0	Absent	Absent	Absent	Absent	Absent	Absent
18	12383	47	F	C	Present	Absent	Absent	Absent	Present	Present(1f)	Present	Absent	2.4	Absent	Absent	Absent	Absent	Absent	Present
19	12401	55	F	NC	Absent	Present	Present	Absent	Absent	Absent	Absent	Present	5.9	Absent	Absent	Absent	Absent	Absent	Absent

20	12403	40	F	NC	Present	Present	Present	Absent	Absent	Absent	Absent	Absent	4.6	Absent	Absent	Absent	Absent	Absent	Absent
21	12408	55	F	NC	Absent	Present	Present	Absent	Present	Absent	Present	Present	4.0	Absent	Absent	Absent	Absent	Absent	Absent
22	12410	39	F	NC	Present	Absent	Absent	Absent	Absent	Absent	Absent	Absent	4.8	Absent	Absent	Absent	Absent	Absent	Absent
23	12413	46	M	NC	Absent	Present	Absent	Absent	Present	Absent	Present	Present	2.4	Absent	Absent	Present	Absent	Absent	Absent
24	12415	55	F	NC	Present	Present	Present	Absent	Absent	Absent	Absent	Present	5.0	Present	Absent	Absent	Absent	Absent	Absent
25	12436	52	F	NC	Absent	Present	Absent	Absent	Present	Absent	Present	Absent	2.0	Absent	Absent	Absent	Absent	Absent	Present
26	12438	40	F	NC	Present	Absent	Absent	Absent	Absent	Absent	Absent	Present	3.2	Absent	Absent	Absent	Absent	Absent	Absent
27	12444	35	F	NC	Present	Absent	Absent	Absent	Absent	Absent	Absent	Absent	1.0	Absent	Absent	Absent	Absent	Absent	Absent
28	12449	45	F	NC	Absent	Present	Present	Absent	Present	Absent	Present	Present	5.4	Present	Absent	Absent	Absent	Absent	Absent
29	12456	30	F	NC	Present	Absent	Absent	Absent	Absent	Absent	Absent	Absent	0.2	Absent	Absent	Absent	Absent	Absent	Absent
30	12462	32	F	NC	Present	Present	Present	Absent	Present	Present(<1f)	Absent	Absent	4.2	Absent	Absent	Absent	Absent	Absent	Present
31	12466	49	F	C	Present	Present	Present	Absent	Present	Present(1f)	Present	Absent	5.0	Present	Absent	Absent	Absent	Absent	Absent
32	12472	27	F	NC	Present	Absent	Present	Absent	Absent	Absent	Absent	Absent	4.6	Absent	Absent	Absent	Absent	Absent	Absent
33	12479	42	F	NC	Present	Absent	Absent	Absent	Absent	Absent	Present	Absent	4.0	Absent	Absent	Absent	Absent	Absent	Absent
34	12481	30	F	C	Present	Absent	Absent	Absent	Present	Present(5f)	Absent	Present	4.5	Absent	Absent	Absent	Absent	Absent	Present
35	12483	61	F	NC	Absent	Present	Present	Absent	Present	Present(<1f)	Present	Absent	4.3	Absent	Absent	Absent	Absent	Absent	Present
36	12493	23	F	NC	Present	Absent	Absent	Absent	Absent	Absent	Absent	Absent	2.3	Absent	Absent	Absent	Absent	Absent	Absent
37	12502	54	F	NC	Absent	Present	Present	Present	Present	Absent	Present	Present	4.0	Absent	Absent	Absent	Absent	Absent	Absent
38	12504	21	F	NC	Present	Absent	Absent	Absent	Absent	Absent	Absent	Absent	2.0	Absent	Absent	Absent	Absent	Absent	Absent
39	12507	22	F	NC	Present	Absent	Absent	Absent	Absent	Absent	Absent	Absent	1.0	Absent	Absent	Absent	Absent	Absent	Absent
40	12519	55	F	NC	Present	Absent	Absent	Absent	Absent	Absent	Absent	Present	4.5	Present	Absent	Absent	Absent	Absent	Absent
41	12533	45	F	NC	Absent	Present	Present	Present	Present	Absent	Absent	Present	1.7	Absent	Absent	Absent	Absent	Absent	Absent
42	12538	55	F	NC	Present	Present	Present	Absent	Absent	Absent	Absent	Absent	1.5	Present	Absent	Absent	Absent	Absent	Absent
43	12551	42	F	NC	Present	Absent	Absent	Absent	Absent	Absent	Absent	Absent	3.0	Absent	Absent	Absent	Absent	Absent	Present
44	12553	30	F	NC	Present	Present	Present	Absent	Present	Absent	Present	Absent	3.0	Present	Absent	Absent	Absent	Absent	Absent
45	12566	40	F	NC	Present	Absent	Absent	Absent	Present	Present	Present	Present	4.3	Absent	Absent	Absent	Absent	Absent	Absent

46	12568	45	F	NC	Present	Absent	Absent	Absent	Absent	Absent	Absent	Absent	3.7	Absent	Absent	Absent	Absent	Absent	Absent
47	12580	49	F	NC	Absent	Present	Present	Absent	Present	Absent	Present	Present	7.3	Absent	Absent	Absent	Absent	Absent	Absent
48	12582	50	F	NC	Present	Present	Present	Present	Present	Absent	Present	Absent	3.0	Absent	Absent	Absent	Absent	Absent	Absent
49	12586	41	F	C	Present	Present	Absent	Absent	Present	Present(5f)	Present	Absent	3.4	Absent	Absent	Absent	Absent	Absent	Present
50	12588	29	M	NC	Present	Absent	Absent	Absent	Absent	Absent	Present	Absent	4.0	Absent	Absent	Absent	Absent	Absent	Absent
51	12605	55	F	NC	Absent	Present	Present	Absent	Present	Absent	Present	Present	6.3	Absent	Absent	Absent	Absent	Absent	Absent
52	12608	52	F	NC	Absent	Present	Present	Absent	Present	Absent	Present	Absent	4.2	Present	Absent	Absent	Absent	Absent	Present
53	12612	36	F	C	Present	Absent	Absent	Absent	Present	Present(6f)	Present	Present	8.7	Absent	Absent	Absent	Absent	Absent	Present
54	12615	29	F	NC	Present	Absent	Present	Absent	Absent	Absent	Absent	Present	5.5	Absent	Absent	Absent	Absent	Absent	Absent
55	12629	24	F	NC	Present	Absent	Absent	Absent	Present	Absent	Present	Absent	4.3	Absent	Absent	Absent	Absent	Absent	Absent
56	12631	32	F	NC	Present	Absent	Absent	Absent	Absent	Absent	Absent	Absent	2.2	Absent	Absent	Absent	Absent	Absent	Absent
57	12632	25	F	NC	Present	Absent	Absent	Absent	Absent	Absent	Absent	Absent	5.0	Absent	Absent	Absent	Absent	Absent	Absent
58	12643	47	F	NC	Present	Present	Present	Absent	Absent	Absent	Absent	Absent	1.3	Absent	Absent	Absent	Absent	Absent	Absent
59	12646	32	F	NC	Present	Absent	Absent	Absent	Present	Absent	Present	Absent	5.2	Absent	Absent	Absent	Absent	Absent	Absent
60	12654	36	F	NC	Present	Absent	Absent	Absent	Absent	Absent	Absent	Absent	4.2	Absent	Absent	Absent	Absent	Absent	Absent
61	12656	46	F	C	Present	Absent	Absent	Absent	Present	Present(3f)	Present	Absent	3.9	Present	Absent	Absent	Absent	Absent	Absent
62	12657	67	F	C	Absent	Present	Present	Absent	Present	Present(3f)	Present	Present	4.4	Present	Absent	Absent	Absent	Absent	Present
63	12663	42	M	NC	Present	Absent	Absent	Absent	Absent	Absent	Absent	Absent	8.6	Absent	Absent	Absent	Absent	Absent	Absent
64	12666	40	F	NC	Present	Absent	Absent	Absent	Absent	Absent	Absent	Absent	1.3	Absent	Absent	Absent	Absent	Absent	Absent
65	12670	43	F	NC	Present	Absent	Absent	Absent	Absent	Absent	Absent	Absent	4.9	Absent	Absent	Absent	Absent	Absent	Absent
66	12672	28	F	NC	Present	Absent	Absent	Absent	Present	Absent	Present	Present	5.8	Absent	Absent	Absent	Absent	Absent	Absent
67	12676	28	F	NC	Present	Absent	Absent	Absent	Absent	Absent	Absent	Absent	1.5	Absent	Absent	Absent	Absent	Absent	Absent
68	12678	47	F	C	Present	Absent	Absent	Absent	Present	Present(3f)	Present	Present	4.5	Absent	Absent	Absent	Absent	Absent	Present
69	12681	55	F	NC	Absent	Present	Present	Absent	Present	Absent	Present	Present	6.8	Present	Absent	Absent	Absent	Absent	Present
70	12684	60	M	NC	Absent	Present	Present	Absent	Present	Absent	Present	Present	4.2	Present	Absent	Absent	Absent	Absent	Absent
71	12707	55	F	NC	Absent	Present	Present	Present	Present	Absent	Present	Present	3.9	Present	Absent	Absent	Absent	Absent	Present